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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/045,178	KASAHARA ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *41,43-46,49-51,56,58,59,61,63-73,75,78-82 and 87-121* is/are pending in the application.

4a) Of the above claim(s) *46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,43-45,49-51,56,58,59,61,63-73,75,78-82 and 87-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-40, 42, 47, 48, 52-55, 57, 60, 62, 74, 76, 77, and 83-86 have been cancelled. Claim 46 has been withdrawn. Claims 41, 43, 66, 80-82, 87, 89, 91, 93, 95, 97, 100-105, 107, 109, 111, 113, 119, and 121 have been amended.

Claims 41, 43-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, and 87-121 are under examination.

2. All rejections pertaining to claim 42 are moot because Applicant cancelled the claim in the reply filed on 08/22/2008.

Specification

3. The disclosure is objected to because of the following informalities: this application contains sequence disclosures (p. 68, lines 9 and 10) that are encompassed by the definitions for nucleotide sequences set forth in 37 CFR 1.821 (a)(1) and (d). However, the specification fails to comply with the requirements of 37 CFR 1.821 (a)(1) and (d), because the sequence identifiers, preceded by SEQ ID NO are missing.

Appropriate correction is required.

4. The disclosure is objected to because of the following informalities: on p. 64, line 10, the specification teaches that one of LTR three regions is U4. However, all figures

in the specification identify this region as U5; the art identifies this region as U5.

Amending the specification to recite "U5" would obviate this rejection.

Response to Arguments

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 41, 43-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, and 87-121 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22, 23, and 26-34 of copending Application No. 11/805,411 in view of both Yan et al. (Prostrate, 1997, 32: 129-139, of record) and Sobol et al. (U.S. patent No. 5,674,486).

It is noted that the instant claims were previously rejected over claims 13-16, 19, 22, 23, 25, and 26 of copending Application No. 11/805,411; however, claims 13-21 and 25 were cancelled in Application No. 11/805,411 (reply filed on 10/09/2008) and new claims 27-34 were added. Cancellation of claims 13-21 and 25 and introduction of the new claims 27-34 does not change the rejection because the application claims recite an *in vivo* method of infecting a mammalian organism with a replication competent virus which is identical to the instant replication competent retrovirus; the specification of Application No. 11/805,411 discloses that the only use of infecting a mammalian organism with the replication competent virus is therapy (p. 2, lines 29-31).

This is a provisional obviousness-type double patenting rejection.

The instant claims are drawn to a method of treating a human subject having a cell proliferative disorder by *in vivo* administering to the subject a recombinant replication competent oncoretroviral polynucleotide or a recombinant replication competent oncoretrovirus, wherein the polynucleotide or virus comprise polynucleotides encoding GAG, POL and envelope (ENV), an oncoretroviral polynucleotide comprising LTRs at the 5' or 3' its ends, a cassette having an IRES operably linked to a heterologous nucleic acid encoding a suicide gene or a cytokine, wherein the cassette is inserted 5' to the 3' LTR and 3' to the polynucleotide encoding ENV and wherein the recombinant replication competent oncoretroviral polynucleotide also comprises cis-acting nucleic acid sequences for reverse transcription, packaging, and integration in a target cells; the expression of the suicide gene is activated by administering a pro-drug and the cytokine could be IL-1 to IL-12 or IFNγ (claims 41-45, 61, 66, 67-69, 78, 81, 82,

87, 95, 97-101, 103-105, 107, 109, 111, 113, 116-119, and 121). The proliferative disorder could be melanoma or glioblastoma (claims 56, 75, 87, 89, 91, 93, and 95), the LTR comprises a tissue specific promoter such as the probasin promoter (claims 58, 59, 88, 90, 92, 94, 96, 106, 108, 110, 112, 114), the ENV is amphotropic or ecotropic (claims 50 and 72) or a chimeric protein comprising a targeting ligand such as an antibody (claims 63-65, 81, 82, 93, 95, 103, 104, 111, and 113) or a non-retroviral envelope (claims 119 and 120). The GAG, POL and ENV are from MoMLV wherein the MoMLV can be amphotropic or ecotropic (claims 49-51, 70, 71, 80, 91, 102, 109, 115-120). With respect to claims 49-51, 70, 80, 91, 102, 109 and 115 it is noted that they recite GAG, POL and ENV from MLV and not MoMLV. However, MLV is not a species but rather a genus comprising several species of murine leukemia viruses among which is Moloney murine leukemia virus (MoMLV). Because the claims do not specifically recite an MLV species and because the only MLV species envisioned by the instant specification is MoMLV, claims 49-51, 70, 80, 91, 102, 109 and 115 are interpreted as being drawn to MoMLV.

The application claims recite a method of *in vivo* infecting an organism administering to the subject a recombinant replication competent retrovirus, wherein the replication competent retrovirus comprises a retroviral GAG coding sequence, a retoviral POL coding sequence, a retroviral ENV coding sequence, an retroviral LTRs sequence, a heterologous coding sequence (such as a suicide gene or other therapeutic sequence) operably linked to a regulatory nucleic acid sequence, one or more sequences for tissue-specific targeting, and a tissue-specific promoter (claims 26-

34). The tropism of the retrovirus is altered (claim 22) and the plasmid is introduced by hydrodynamic transfection (claim 23). The specification defines the recombinant replication competent oncoretroviral polynucleotide is from MoMLV (i.e., GAG, POL and ENV are derived from MoMLV), that ENV can be amphotropic or ecotropic, and that the heterologous sequence encoding the therapeutic protein is operably linked to the regulatory nucleic acid sequence via an IRES, wherein the IRES and the heterogeneous gene form a cassette which is located 5' to the 3' LTR and 3' to the sequence encoding ENV (p. 1, paragraph 0017, p. 8, paragraph 0117, Fig. 1). The specification also discloses that the heterologous therapeutic sequence is a cytokine (such as interleukins), that the virus comprises sequences required for its production within the transfected cell (i.e., cis-acting nucleic acid sequences for reverse transcription, packaging, and integration in a target cells), the tropism of the virus is altered by using a chimeric protein ENV-antibody (i.e., targeting sequence) or a non-retroviral envelope such as that of VSV or CMV (p. 4, paragraphs 0054, 0058-0061 and 0064, p. 5, paragraph 0067, p. 8, paragraphs 0114, 0116, 0117, and 0119). The specification also defines that the replication competent retrovirus is suitable to treat cancer (p. 3, lines 7-13). Since melanoma or glioblastoma are forms of cancer, one of skill in the art would have known to use the recombinant retrovirus of the Application No. 11/805,411 to treat them. The application claims do not disclose the probasin promoter. However, at the time of filing the probasin promoter was known and used in the prior art, for example the probasin promoter was used by Yan et al. to target gene expression in the prostrate (Abstract, p. 130, columns 1 and 2, p. 133, column 2).

Therefore, one of skill in the art would have known to use the probasin promoter to specifically target the suicide genes to prostrate tumors for increased treatment efficiency of such tumors. With respect to the limitations recited in the instant claims 116-118, it is noted that the art teaches cancer therapy by using a variety of cytokine, including IFNγ (see Sobol, Abstract, column 4, lines 25-27). It would have been obvious to one of skill in the art, at the time the invention was made to use a gene encoding IFNγ to achieve the predictable result of treating cancer.

Since claims 22, 23, and 26-34 of copending Application No. 11/805,411 embrace all limitations of the instant claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, 87-121, the application claims and the instant claims are obvious variants of one another.

Applicant traversed the instant rejection on the grounds that the rejection relies heavily on the primary reference being prior art. However, Applicant argues, the '411 application is not prior art to the present application. Applicant points out that the earliest priority date of the '411 application is November 24, 2004, while the present application claims priority, as a continuation, to October 1, 1999, which claims priority to provisional application filed October 1, 1998 (more than 5 years prior to the '411 applications earliest priority date). Applicant argues that the non-statutory obviousness-type double patenting rejection is citing an application (the '411 application) as prior art, when in fact it is not. Applicant asserts that the policy behind a non-statutory obviousness rejection is to determine whether there is a time-wise extension of the

claimed subject matter (i.e., the subject matter claimed in the present application) compared to the cited reference (i.e., the '411 application) (MPEP 804). Applicant argues that there can be no time-wise extension of the present application beyond that of the '411 application; the present application, by statute (absent any patent term adjustments), will expire prior to the cited '411 application. Furthermore, Applicant argues, MPEP 804 indicates that the Examiner that an "one-way obviousness" test is applicable only when the application being rejected is the later filed application or both are filed on the same day; the test is applied based upon whether a claim pending in the "application at issue" would be anticipated by, or obvious in view of, an earlier filed application. Applicant argues that the use of this test by the Examiner is in error in the present case because the present application is the earlier filed application and thus this test does not apply. Thus, Applicant argues, the primary reference (i.e., the '411 application) is not prior art and the rejection should be withdrawn.

Applicant's arguments are acknowledged however, the rejection is maintained for the following reasons:

The instant rejection is a double patenting and not an art rejection and therefore, the '411 is not art. A double patenting rejection can be made between two pending applications regardless of their filing date; such a rejection should be made in each application as long as their claims are conflicting unless the provisional double patenting rejection is the only rejection remaining in at least one of the applications (see 804 [R-5]). It is noted however, that the provisional double patenting rejection is not the only rejection remaining in the instant case (see below).

Applicant argues that the one-way obviousness type is applicable only when the application being rejected is the later filed application or both are filed on the same day and that the Examiner improperly applied the one-way obviousness test in the instant case. This argument is not found persuasive because the one-way obviousness type is also applicable when the application being rejected is the earlier filed application. The following is a citation from MPEP 804 [R-5]:

> b) One-Way Obviousness
>
> Similarly, even if the application at issue is the earlier filed application, only a one-way determination of obviousness is needed to support a double patenting rejection in the absence of a finding: (A) of administrative delay on the part of the Office causing delay in prosecution of the earlier filed application; and (B) that applicant could not have filed the conflicting claims in a single (i.e., the earlier filed) application.
>
> b) Two-Way Obviousness
>
> If the patent is the later filed application, the question of whether the timewise extension of the right to exclude granted by a patent is justified or unjustified must be addressed. A two-way test is to be applied only when the applicant could not have filed the claims in a single application and there is administrative delay. In re Berg, 46 USPQ2d 1226 (Fed. Cir. 1998) ("The two-way exception can only apply when the applicant could not avoid separate filings, and even then, only if the PTO controlled the rates of prosecution to cause the later filed species claims to issue before the claims for a genus in an earlier application . . . In Berg's case, the two applications could have been filed as one, so it is irrelevant to our disposition who actually controlled the respective rates of prosecution."). In the absence of administrative delay, a one-way test is appropriate. In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993) (applicant's voluntary decision to obtain early issuance of claims directed to a species and to pursue prosecution of previously rejected genus claims in a continuation is a considered election to postpone by the applicant and not administrative delay). Unless the record clearly shows administrative delay by the Office and that applicant could not have avoided filing separate applications, the examiner may use the one-way obviousness determination and shift the burden to applicant to show why a two-way obviousness determination is required.

In the instant case there is no record of administrative delay by the Office nor is there a showing that Applicant could not have avoided filing separate applications.

Therefore, the Examiner properly applied the one-way obviousness test and the rejection is maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. (Cancer Research, 1993, 53: 83-88), in view of each Martuza et al. (U.S. Patent No. 5,585,096), Murakami et al. (Gene, 1997, 202: 23-29), and Sobol et al. (U.S. patent No. 5,674,486).

Claims 49-51, 70, 80, 91, 102, 109 and 115 recite GAG, POL and ENV from MLV and not MoMLV. However, MLV is not a species but rather a genus comprising several species of murine leukemia viruses among which is Moloney murine leukemia virus (MoMLV). Because the claims do not specifically recite an MLV species and because the only MLV species envisioned by the instant specification is MoMLV, claims 49-51, 70, 80, 91, 102, 109 and 115 are interpreted as being drawn to MoMLV.

Ram et al. teach a method of treating glioblastoma (i.e., a cell proliferative disorder) in rats by the *in vivo* intratumoral administration of a therapeutically effective amount of cells producing a retrovirus comprising 5' and 3' long terminal repeats (LTR) and a heterologous nucleic acid sequence encoding the HSV thymidine kinase (tk) (i.e., a suicide gene) that uses the 5' LTR as its promoter (i.e., operably linked to a regulatory nucleic acid sequence), followed by contacting the rats with ganciclovir (i.e., a prodrug), wherein the ganciclovir is activated by the tk expression; since the cells are administered to the animal, they must necessarily be administered in a pharmaceutically acceptable carrier (i.e., the retrovirus is contained in a pharmaceutically acceptable carrier) (claims 41, 44, 45, 66, 78, 79, 87, 89, 97, 100, 105, 107, 119, and 121) (Abstract, p. 83, columns 1 and 2, p. 84, column 1, p. 85, column 2). Ram et al. teach that the retroviral vector is MoMLV, i.e., a mammalian oncoretrovirus (claims 49, 61, 70, 80, 91, 99, 102, 109, and 115) (p. 83, column 1). Ram et al. teach their approach as suitable for the treatment of localized tumors in humans (Abstract, p. 83, column 2, second full paragraph, p. 88, column 1).

Ram et al. teach administering cells producing replication deficient MoMLV and not a replication competent retrovirus, as recited by the instant claims 41, 66, 80, 87, 89, 91, 97, 100, 102, 105, 107, 109, 119, and 121. However, at the time of filing, the advantages of using replication competent retroviruses for cancer treatment was taught by the prior art. For example, Martuza et al. teach that the administration of replication deficient viruses or of cells producing replication deficient viruses is not applicable to the treatment of tumors in humans because, since the virus cannot replicate, gene transfer

occurs within a few cell-distances, which leads to inefficient gene delivery; for these reasons, Martuza et al. suggest the use of replication competent viral vectors (including retroviral vectors) (column 2, lines 1-45, column 5, lines 14-18). Martuza et al. teach that such replication competent viruses can be used to treat melanoma (claims 56, 75, 98, and 101) (column 3, lines 52-55). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al. by using a replication competent MoMLV (i.e., an oncoretrovirus comprising MoMLV GAG, POL, ENV, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration into a target cell), with a reasonable expectation of success. The motivation to do so is provided by Martuza et al., who teach the necessity to replace replication deficient viruses with replication competent viruses for efficient gene therapy in animals and humans. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that replication competent viruses can be successfully obtained and used for cancer treatment. With respect to the limitation of the MoMLV being an amphotropic MoMLV (claims 50 and 71), since the teachings of Ram et al. and Martuza et al. (U.S. Patent No. 5,585,096) disclose MoMLV suitable for therapy in humans, their MoMLV must necessarily be amphotropic (i.e., allows transduction of cells of other species than the mouse).

Ram et al. and Martuza et al. do not teach a cassette comprising an internal ribosome entry site (IRES) operably linked to the suicide gene, wherein the cassette is located 5' to the 3' LTR and 3' to the sequence encoding ENV (claims 41, 66, 80, 87,

89, 91, 97, 100, 102, 105, 107, 109, 119, and 121). However, at the time of filing the use of cassettes comprising IRES operably linked to heterologous genes was known in the prior art, for example Murakami et al. teach insertions of such cassettes into retroviral vectors, wherein the cassettes are inserted 5' to the 3' LTR and 3' to the sequence encoding ENV (p. 25, Fig. 1A). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al. and Martuza et al. by inserting an IRES-suicide gene cassette in their MoMLV, as taught by Murakami et al., with a reasonable expectation of success. The motivation to do so is provided by Murakami et al. who teach that introduction of such IRES cassettes 5' to the 3' LTR and 3' to the sequence encoding ENV results in increased expression of heterologous genes as compared to the vectors lacking the IRES cassettes (Abstract, p. 23, column 2, last paragraph, p. 28, column 2, first full paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing so because Murakami et al. teach that IRES cassettes can be successfully inserted into retroviral vectors.

With respect to the limitation of a viral vector encoding a cytokine (claims 97, 100, 102, 105, 107, 109, and 119), Martuza et al. teach tumor killing by using replication competent viruses lacking a suicide gene and comprising a gene encoding a cytokine, wherein tumor killing is enhanced by cytokine expression in the tumor (column 11, lines 35-55). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made to substitute the suicide gene with a gene encoding a cytokine to achieve the predictable result of killing tumor cells. With respect to the limitations

recited in claims 116-118, it is noted that the art teaches cancer therapy by using a variety of cytokine, including IFNγ (see Sobol, Abstract, column 4, lines 25-27). It would have been obvious to one of skill in the art, at the time the invention was made to use a gene encoding IFNγ to achieve the predictable result of treating cancer.

With respect to the limitation of treatment by using a recombinant replication competent oncoretrovirus (instant claims 41, 80, 81, 87, 91, 93, 97, 102, 103, 105, 109, and 119), it is noted that the administration of the replication competent MoMLV to a patient would necessarily result in the *in vivo* production of the virus, and therefore, the combined teachings above embrace a method of treatment by using a recombinant replication competent MoMLV.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that the claimed invention is not a mere combination of old elements but a combination that results in a system that functions in a different manner resulting in unexpected genetic stability and usefulness of the RCR vectors; this type of advancement in the technology should be rewarded based upon the public policies of the Patent System. Applicant notes that, through extensive experimentation and development, he demonstrates that not just any combination of elements (as suggested by the Office Action), not just any insertion site (as suggested by the Office Action) and not just any viral vector (as suggested by the Office Action) would result in the claimed invention. Applicant argues that he was the

first to discover that the combination of virus selection and IRES cassette insertion site provides a competent, stable and effective RCR system for treating cell proliferative disorders (Applicant cites Logg et al., J. Virol., 2001, 75: 6989-6998, as setting forth the importance of the cassette location). Applicant argues that the combination of transduction efficiency, transgene stability and target selectivity was unknown in any recombinant replication competent mammalian oncoretrovirus prior the instant vector; the methods (and the vector composition used in the methods) provides insert stability and maintains transcription activity of the transgene and the translational viability of the encoded polypeptide.

Applicant argues that the Examiner uses hindsight in making the instant rejection and that the Examiner fails to appreciate that in 1998 (the priority date of the instant application), the state of the art was (i) replication defective vectors (Ram et al.), (ii) that replication competent vectors with transgenes were unstable, (iii) that vectors in use were incapable of mammalian infectivity (Murakami et al.) or (iv) that vector in use were based on DNA viruses (Martuza et al.). Applicant argues that the cited references either individually or in combination do not provide the necessary factors to set forth a *prima facie* case of obviousness. To put the combination of the cited references in context and to demonstrate the lack of a *prima facie* case of obviousness, Applicant submits that he describes each reference individually and then in combination.

With respect to Ram et al., Applicant argues that **(i)** they fail to teach or suggest a recombinant replication competent oncoretroviral vector or recombinant plasmid or recombinant polynucleotide encoding a replication competent oncoretroviral vector, **(ii)**

they fail to teach or suggest treating a tumor in the absence of a helper cell to assist in the defective viral replication, **(iii)** they fail to teach or suggest a cytokine transgene, **(iv)** they fail to teach or suggest a chimeric ENV protein, **(v)** they fail to teach or suggest a tissue specific promoter, and **(vi)** they fail to teach or suggest an IRES cassette. Therefore, Applicant argues, the teachings of Ram et al. are far removed from the instant invention, which utilize a replication competent, non-helper cell system to treat a cell proliferative disease or disorder. Applicant points out that Ram et al. describe a method which utilizes "retroviral producer cells" injected at the site of a tumor (see page 86, column 2, last paragraph of the cited reference), wherein the producer cells support the in situ production of a retroviral vector containing a suicide gene and wherein the producer cells are necessary because the vector is not replication competent. Further, Applicant argues, the nucleic acid sequence encoding the suicide gene is located "just downstream of the 5' long terminal repeat sequence" (see page 84, column 1, lines 2-4 of the cited reference). Applicant submits that it is clear from the contents of the cited reference that Ram et al. fail to appreciate the significance of utilizing a replication competent oncoretrovirus in the absence of a producer cell to achieve efficient transduction. Because Ram et al. use a gutted vector Applicant argues, transcription of a transgene can easily be effected by the 5'LTR; in contrast, Applicant's transgene is not directly linked to the 5'LTR. Applicant submits that the location of the transgene and the preceding IRES as set forth in the instant claims is not insignificant. Thus, Applicant argues, Ram et al. is deficient in at least three aspects: **(i)** the vector is replication defective, **(ii)** the methods require a helper cell, and **(iii)** the transgene location is of little

or no important to Ram et al. Applicant continues arguing that, in order to overcome the deficiencies of Ram et al., the Examiner combines Ram et al. with Martuza et al.

With respect to Martuza et al., Applicant argues that they teach replication competent viral vectors derived from adenovirus and herpes simplex virus (such vectors are DNA vectors - very different than RNA vectors). Applicant argues that it is not clear why one would combine a defective retrovirus with a DNA virus, when the genomes are completely different. Even if the references are combined, Applicant argues, the combination still fails to teach or suggest the claimed invention because, like Ram et al., Martuza et al. fail to appreciate the importance of positioning a heterologous sequence encoding a therapeutic polypeptide in a region outside the LTR or not linked directly to the LTR of the viral vector; nor does the combination of references teach, suggest, or appreciate an internal ribosome entry site. Applicant argues that merely inserting a transgene into a replication competent retrovirus does not provide a reasonable expectation that infectivity, stability or continued transmission and expression of the transgene will occur. Applicant submits that numerous peer-reviewed journal articles indicate that insertion of transgene into U3 and other locations within a replication competent retrovirus can cause a loss of replication, and genetic instability of the vector (see, e.g., Logg et al. supra). Thus, Applicant argues, the combination of Ram et al. and Martuza et al. fail to teach or suggest Applicants' claimed invention and do not provide any reasonable expectation of success in achieving a RCR having the transmission and genetic stability of the claimed invention.

With respect to Murakami et al., Applicant argues that they use a Rous Sarcoma Virus (RSV); the IRES-transgene insertions described in Murakami et al. consist of an IRES-transgene sequence positioned 3' to the env-encoding sequence and 5' to the 3' LTR. However, Applicant argues, the cited reference utilizes replication competent avian sarcoma viruses (RCAS) which are distinct from the oncoretroviruses of the pending claims and incapable of replication in mammalian cells. Thus, the RSV vector of Murakami et al. could not be used to treat a mammal as set forth in Applicant's claims (Applicant points out that the inability of RSV to produce infective viral particles in mammalian cells is disclosed in several peer-reviewed journal articles). Applicant argues that the Examiner makes a leap from a defective gutted retroviruses, to DNA viruses to avian viruses, with little direction, suggestion or likelihood of success in the art; it is only through Applicant's disclosure and hindsight reconstruction that such very different viral architectures and functions can be pieced together. For example, the Office alleges that it would be a simple matter of substituting one viral type for another, however, this statement fails to address the many other factors which would lead one of skill in the art away from such combinations. For example, avian RSV naturally carries extra sequences (the src oncogene, which is in addition to the gag, pol and env genes required for replication, and which is similar in size to the env gene) positioned just after env. Thus, RSV evolved a capacity to incorporate a large piece of extra sequence in this location in its genome, something not found in mammalian oncoretroviruses. The idea of putting an IRES-transgene insert after the env gene in a mammalian oncoretrovirus would not be obvious in view of the cited references simply because

there are no known naturally-evolved replication-competent mammalian oncoretroviruses with extra genes following the env (or anywhere else, for that matter). In fact, it was recognized in the art that inserting a transgene in the region following the env gene although providing short term expression ultimately resulted in genetic instability and loss of the transgene in subsequent rounds of replication. RSV through natural development has developed a "transgene insertion site" because it contained a non-essential and replaceable gene (src), thus providing additional flexibility compared to mammalian oncoretroviruses. One of skill in the art would have not recognized, prior to Applicant's invention, insertion of an IRES transgene cassette into a replication-competent MLV vector at the claimed location because MLV and other mammalian oncoretroviruses were known to not have such dispensable genes and therefore not have the same flexibility known to RSV; one of skill in the art would not have looked to MLV, for example, because there are not any parts of the MLV genome that are known to be dispensable. Further, Applicant argues, combining the IRES-transgene of Murakami et al. and the vector described by Martuza et al. would not result in a vector or method described or claimed in the instant application. It is not clear why or how one would combine a DNA viral vector and an RNA viral vector. Furthermore, there would be no reasonable expectation of success of merely inserting a sequence immediately downstream of the env gene in an HSV genome without disruption of the viral life cycle.

With respect to Sobol et al., Applicant argues that they actually teach that one should avoid the use of replication competent retroviruses. For examples, Sobol et al. teach throughout the specification that one should use proper screening, production and

removal of replication competent retroviruses from any system or method. Applicant submits that the Examiner appears to view Sobol et al. with respect to only "certain" teachings in the reference and fail to recognize the more important teaching away of the reference in that one should avoid replication competent retroviruses. However, even in view of such a teaching away, Sobol et al. do not remedy the deficiencies as set forth above regarding the replication competent retrovirus and use of such recombinant viral vectors for the treatment of cell proliferative disorders.

Applicant argues that not only do the cited references when combined fail to identify predictable solutions for achieving a replication competent oncoretrovirus capable of delivering a therapeutic polypeptide, they also fail to provide all the components necessary for the production of the vector set forth in the claimed methods. Applicant argues that the surprising combination of transduction efficiency, transgene stability, and target selectivity provided by the claimed invention were simply unknown in any recombinant replication competent mammalian oncoretrovirus prior to the invention. For these reasons, Applicant submits that the pending claims are novel and non- obvious over the cited references and requests the withdrawal of the rejection.

Applicant's arguments are acknowledged however, the rejection is maintained for the following reasons:

In response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was

within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant submits that he describes each reference individually and then in combination. It is noted however, that Applicant does not address the combination of all the cited references. Applicant only discusses the combination of Ram et al. and Martuza et al. or the combination of Murakami et al. and Martuza et al. But it is the combination of all of the cited references which renders the claimed invention *prima facie* obvious. While it is true that none of the references teaches each and every limitation of the instant claims, Applicant is reminded that such is not a requirement for an obviousness-type rejection. Had any of the cited references taught each and every claim limitation, the rejection would have been an anticipation rejection and not an obviousness-type rejection. An obviousness-type rejection takes into consideration the knowledge available to one of skill in the art at the time the claimed invention was made. Therefore, Applicant's argument that the primary reference (i.e., Ram et al.) fails to appreciate the significance of utilizing a replication competent oncoretrovirus in the absence of a producer cell to achieve efficient transduction is not found persuasive;

using such was taught and suggested by the prior art, which teaches the advantages of using replication competent viruses for therapy as opposed to replication defective viruses. The motivation to modify the method of Ram et al. by using a replication competent retrovirus is provided by the prior art. For example, Martuza et al. teach that the administration of replication deficient viruses or of cells producing replication deficient viruses (i.e., as in Ram et al.) is not applicable to the treatment of tumors in humans because, since the virus cannot replicate, gene transfer occurs within a few cell-distances, which leads to inefficient gene delivery; Martuza et al. teach the necessity to replace replication deficient viruses with replication competent viruses for efficient gene therapy in animals and humans (see the rejection above). Applicant argues that it is not clear why one would combine a defective retrovirus with a DNA virus, when the genomes are completely different. This argument is not found persuasive because the instant rejection is not based on combining an RNA virus with a DNA virus; the Examiner never proposed such. Martuza et al. was cited for teaching the advantages of using replication competent viruses as opposed replication incompetent viruses; these teachings are pertaining to both DNA and RNA viruses, such as retroviruses (see column 2, lines 1-45). Therefore, the rejection is based on modifying Ram et al. by replacing their replication incompetent retrovirus with its replication competent variant, as suggested by Martuza et al. It is noted that replication competent retroviruses were all known and used in the prior art (see the teachings of Martuza et al. above); therefore, one of skill in the art would have had a reasonable expectation of success in modifying Ram et al. according to the teachings of Martuza et

al. Applicant also argues that the combination of Ram et al. and Martuza et al. does not provide any reasonable expectation of success in achieving a replication competent retrovirus having the transmission and genetic stability of the claimed invention. Again, it is the combination of all cited references, and not only the combination of Ram et al. and Martuza et al., which teaches and provides a reasonable expectation of success in achieving the claimed invention. While the combination of Ram et al. and Martuza et al. does not teach a cassette comprising an internal ribosome entry site (IRES) operably linked to their suicide gene, wherein the cassette is located 5' to the 3' LTR and 3' to the sequence encoding ENV, such was taught and widely used in the prior art (see the teachings of Murakami et al. above). Importantly, Murakami et al. do teach that introduction of IRES cassettes 5' to the 3' LTR and 3' to the sequence encoding ENV results in increased and stable expression of heterologous genes as compared to the vectors lacking the IRES cassettes (Abstract, p. 23, column 2, last paragraph, p. 26, Fig. 2, p. 27, column 2, first full paragraph). Therefore, the benefits of inserting an IRES-comprising cassette cassettes 5' to the 3' LTR and 3' to the sequence encoding ENV was taught by the prior art and Applicant's arguments that the prior art does not recognize the importance of cassette location and that he was the first to discover such are not found persuasive. Applicant argues that Murakami et al. use a replication competent avian sarcoma virus which is distinct from the oncoretroviruses of the pending claims and incapable of replication in mammalian cells and therefore, it could not be used to treat a mammal as set forth in Applicant's claims. This argument is not found persuasive because the instant rejection is not based on replacing the retrovirus

of Ram et al. with the avian retrovirus of Murakami et al.; the rejection is based on modifying the oncoretrovirus of Ram et al. (i.e., capable of replicating in mammalian cells) by including in an IRES-comprising cassette, as taught by Murakami et al. Applicant argues that, because the replication competent avian sarcoma virus of Murakami et al. is distinct from the oncoretrovirus of Ram et al., one of skill in the art would have not recognized, prior to Applicant's invention, that the teachings of Murakami et al. can be extrapolated to the oncoretrovirus of Ram et al. Specifically, Applicant argues that one of skill in the art would not have recognized that an IRES cassette could be inserted into an MLV vector because, unlike the replication competent avian sarcoma virus of Murakami et al., there are not known dispensable parts in the MLV genome. Such is just an argument not supported by any evidence. Applicant did not provide any evidence that replication competent oncoretroviruses cannot incorporate heterologous nucleic acids. In fact, the prior art provides ample examples of gene delivery (including IRES-comprising cassettes) via using replication competent retroviruses such as MLV; the prior art teaches that insertion of IRES-comprising cassettes is compatible with the retroviral replication cycle and allows expression of multiple coding regions from a single promoter (Coffin et al., Retroviruses, Principle of Retroviral Vector Design, Cold Spring Harbor Laboratory Press, 1997; see the entire reference). Additionally, the prior art teaches insertion of the IRES-comprising cassettes 3' to their ENV and 5' to the 3'LTR (see Stull et al., U.S. Patent No. 6,322,969, Fig. 2 and 4, column 14, lines 25-41, column 24, lines 15-27). Clearly, MLV can incorporate IRES-transgenes cassettes 3' to ENV.

Applicant argues that combining the IRES-transgene of Murakami et al. and the vector described by Martuza et al. would not result in a vector or method described or claimed in the instant application. Again, the rejection is not based on modifying the vector of Martuza et al. by introducing the IRES-transgene of Murakami et al. The invention is based on modifying the method of Ram et al. by replacing their replication incompetent MLV vector with a replication competent and IRES-comprising MLV vector (see the rejection above).

With respect to Sobol et al., Applicant argues that they teach away from the instant invention because they teach avoiding replication competent viruses. In response to this argument, it is noted that MPEP clearly states that a teaching away from the invention is a teaching which renders prior art unsatisfactory for the intended purpose (MPEP 2145 [R-6] X D). The reference was cited because it teaches cancer therapy by using a variety of cytokine, including IFNγ. Similar to Ram et al., Sobol et al. teach cancer therapy by administering cells producing replication deficient retroviral vector (Abstract, column 2, lines 17-67, Example 1). However, as noted above, the prior art teaches the necessity of replacing the cells producing replication deficient retroviral vectors with replication competent vectors for gene therapy (see the teachings of Martuza et al. above). Even Sobol et al. teach that murine replication competent retroviruses (i.e., MLV) are not harmful for humans (column 5, lines 23-31). Clearly, the art does not teach that the use of replication competent viruses is unsatisfactory for gene therapy. Therefore, the argument that Sobol et al. teach away from the claimed invention is not found persuasive. With respect to the argument that Sobol et al. do not

remedy the deficiencies of the other references, it is noted that Sobol et al. do not need to do such because there are no deficiencies to be remedied. Ram et al. taken with Martuza et al. and Murakami et al. already teach using replication competent MLV comprising IRES cassettes to treat cell proliferative disorders (see above).

In conclusion, the combination of the cited references provides all the components necessary for the production of the claimed vector. Moreover, the vector taught by the combined references above exhibits high transduction efficiency and transgene stability (see the teachings of Murakami et al. above). With respect to selectivity, MLV exhibits intrinsic tumor selectivity because it cannot infect quiescent cells. Therefore, all features resulting from the insertion of the IRES cassette 3' to ENV and 5' to the 3'LTR were already taught by the prior art and Applicant's argument that he was the first to demonstrate such, as demonstrated by Logg et al., is not found persuasive. It is also noted that Logg et al. do not provide more that what it was already known in the art (i.e., Murakami et al.).

For the reasons set forth above, the rejection is maintained.

9. Claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of Douar et al. (Gene Ther, 1996, 3: 789-796, Abstract).

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91,

97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza et al., Murakami et al., and Sobol et al. do not teach a non-retroviral envelope, such as that of VSV (claims 119 and 120). Douar et al. teach VSV-G pseudotyped MoMLV (Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by using a VSV-G pseudotyped MoMLV, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Douar et al. teach that VSV-G pseudotyped MoMLV has a broader host range. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that VSV-G pseudotyped MoMLV can be successfully obtained and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that Douar et al. do not overcome the deficiencies of the prior references.

Applicant's argument is acknowledged however, the argument is not found persuasive and the rejection is maintained for reasons set forth above.

10. Claims 41, 43-45, 49-51, 56, 58, 59, 61, 66, 70, 71, 73, 75, 78-80, 87-92, 97-102, 105-110, 115-119, and 121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol

et al., in further view of both Vile et al. (Virology, 1995, 214: 307-313) and Yan et al. (Prostrate, 1997, 32: 129-139).

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza et al., Murakami et al., and Sobol et al. do not teach an LTR comprising a tissue-specific promoter (claims 58, 88, 90, 92, 106, 108, and 110). Vile et al. teach a MoMLV vector wherein the LTR comprise the tissue specific tyrosinase promoter, wherein the tyrosinase promoter specifically targets viral gene expression in melanoma cells (Abstract, p. 308, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector in the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by introducing the tyrosinase promoter, within the LTR, with a reasonable expectation of success. One of skill in the art would have been motivated to use the tyrosinase promoter in order to target the expression of the suicide gene in melanoma cells. One of skill in the art would have been motivated to insert the tyrosinase promoter within the LTR because Vile et al. teach that inserting the tissue specific promoters within the LTR abolishes the promoter interference effects observed with retroviral vector wherein the tissue specific promoters are internally inserted (Abstract, p. 307, columns 1 and 2). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that promoters can be successfully introduced within the LTR.

Ram et al., Martuza et al., Murakami et al., Sobol et al., and Vile et al. do not

teach the probasin promoter (claim 59). However, at the time of filing the probasin promoter was known and used in the prior art, for example the probasin promoter was used by Yan et al. to target gene expression in the prostrate (Abstract, p. 130, columns 1 and 2, p. 133, column 2). Therefore, one of skill in the art would have known to use the probasin promoter to specifically target the suicide genes to prostrate tumors for increased treatment efficiency of such tumors.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that none of Ram et al., Martuza et al., Murakami et al., or Sobol et al teach or suggest tissue specific promoters. Applicant argues that, although Vile et al. is combined for teaching a retroviral vector comprising a tissue specific promoter, the retroviral vector of Vile et al. lacks the ENV and is replication defective. Thus, Applicant argues, there could be no insertion of an IRES cassette 3' to the ENV gene or 5' to the 3' LTR as recited in the instant claims. Thus, Applicant argues that the combination of reference fails to teach and suggest a replication competent retrovirus comprising and IRES cassette (optionally a cytokine transgene or suicide gene transgene; optionally a tissue specific promoter) capable of infecting and retaining stability and transmission in mammalian cells. With respect to Yan et al., Applicant argues that, although they teach a probasin promoter, they do not teach or suggest retroviral vectors and do not overcome the deficiencies of the prior references. Furthermore, Applicant argues, a publication by

Logg et al. (J. of Virol., 2002, 76:12783-12791), which is not prior art to the present application, describes that the dual androgen response element promoter functions a 1000 fold better than the wild-type promoter; such unexpected replication efficiency would not have been apparent to someone of skill in the art, further demonstrating the importance of the vectors and methods of the disclosure.

Applicant's arguments are acknowledged however, the rejection is maintained for the following reasons:

The combination of Ram, Martuza et al., and Murakami et al. teaches and suggests a replication competent retrovirus comprising and IRES cassette capable of infecting and retaining stability and transmission in mammalian cells (see above). Applicant argues that, since the retroviral vector of Vile et al. lacks the ENV, there could be no insertion of an IRES cassette 3' to the ENV gene, is not found persuasive. The rejection is based on using a tissue-specific promoter in a vector which already has the IRES cassette 3' to ENV. Beside an argument, Applicant did not provide any evidence that the teaching of tissue-specific promoters could not be extrapolated to retroviral vectors. In fact, the use of tissue-specific promoters in conjunction with expression vectors of any type was routine in the prior art; therefore, one of skill in the art would have expected to have success in modifying Ram, Martuza et al., and Murakami et al. by replacing their promoter with a tissue-specific promoter. Similar considerations apply to Yan et al.; probasin is a prostrate-specific promoter and one of skill in the art would have known and would have expected to be successful is using probasin promoter in the vector of Ram, Martuza et al., and Murakami et al. to target gene expression in the

prostrate when needed. Applicant's argument that Yan et al. do not teach retroviral vectors is irrelevant. Again, the use of tissue-specific promoters (including the probasin promoter) was routine in the prior art. Applicant argues that Logg et al. (J. of Virol., 2002, 76:12783-12791) demonstrate unexpected efficiency of the dual androgen response element promoter (i.e., a synthetic version of the probasin promoter) as compared to the wild-type probasin promoter. This argument is not found persuasive because, not only Logg et al. is a post-filing reference (i.e., at the time of filing there was no evidence of unexpected results), but the claims do not recite dual androgen response element promoter, nor does the specification contemplate to us of such. For these reasons, the rejection is maintained.

11. Claims 41, 43-45, 49-51, 56, 58, 61, 63-73, 75, 78-82, 87-119, and 121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of both Kasahara et al. (Science, 1994, 266: 1373-1376) and Vile et al.

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza, Martuza et al., Murakami et al., and Sobol et al. do not teach a chimeric envelope, wherein the chimeric protein comprises a targeting ligand such as a receptor ligand (claims 63-65, 67-69, 73, 81, 82, 93, 95, 103, 104, 111, and 113) or an ecotropic envelope (claim 72). Kasahara et al. teach tissue specific targeting of MoMLV retroviral vectors to cells

expressing the erythropoietin (EPO) receptor by engineering the vector to encode a chimeric ecotropic MoMLV protein, wherein the chimeric envelope protein comprises EPO (p. 1373, column 2, p. 1374, column 3 bridging p.1375). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by engineering their vector to encode an ecotropic envelope fused to a receptor ligand, with a reasonable expectation of success. The motivation to do so is provided by Kasahara et al., who teach that such viruses can be used to specifically infect human cells expressing the receptor for the ligand and that such a strategy can be used for the treatment of cancer (p. 1373, column 1, p. 1375, column 1 bridging column 2, and column 3). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that such engineered retroviruses can be successfully made and used.

Ram et al., Martuza et al., Murakami et al., Sobol et al., and Kasahara et al. do not teach an LTR comprising a tissue-specific promoter (claims 58, 88, 90, 92, 94, 96, 106, 108, 110, 112, and 114). Vile et al. teach a MoMLV vector wherein the LTR comprise the tissue specific tyrosinase promoter, wherein the tyrosinase promoter specifically targets viral gene expression in melanoma cells (Abstract, p. 308, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector in the method of Ram et al., Martuza et al., Murakami et al., Sobol et al., and Kasahara et al., by introducing the tyrosinase promoter, within the LTR, with a reasonable expectation of success. One of skill in the art would have been

motivated to use the tyrosinase promoter in order to target the expression of the suicide gene in melanoma cells. One of skill in the art would have been motivated to insert the tyrosinase promoter within the LTR because Vile et al. teach that inserting the tissue specific promoters within the LTR abolishes the promoter interference effects observed with retroviral vector wherein the tissue specific promoters are internally inserted (Abstract, p. 307, columns 1 and 2). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that promoters can be successfully introduced within the LTR.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that none of the cited references demonstrate or provide a method of treating cell proliferative diseases by using a replication competent retrovirus comprising an IRES cassette and transgene in mammalian systems. Applicant argues that Kasahara et al. do not teach the IRES cassette as set forth in the methods of the claimed invention capable of infecting mammalian cells. Accordingly, Applicant argues, Kasahara et al. in combination with any and all of the cited references fails to teach or suggest the claimed invention as a whole.

Applicant's arguments are acknowledged however, the rejection is maintained for the following reasons:

In response to Applicant's argument that none of the cited references demonstrate or provide a method of treating cell proliferative diseases by using a replication competent retrovirus comprising an IRES cassette and transgene in mammalian systems, it is noted that this is an obviousness-type rejection and therefore none of the reference has to teach all the limitations recited in the claims. As demonstrated above, the combination of Ram et al., Martuza et al., Murakami et al., and Sobol et al. renders the claimed vector and method *prima facie* obvious. The use of chimeric envelopes was routine in the prior art to and Kasahara et al. was cited as one of the examples demonstrating that chimeric envelopes could be used to specifically infect the cells of interest (see above). Because the use of chimeric envelope was routine, one of skill in the art would have expected to have reasonable success in using such in the vector of Ram et al., Martuza et al., Murakami et al., and Sobol et al. For these reasons, Applicant's arguments are not found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 112, new matter

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 41, 43-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, 87-121 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written

description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the amendment to the claims to include the recitation that the retroviral polynucleotide comprises LTRs "at the 5' or 3'" ends is considered new matter. The amendment was filed on 10/31/2007.

In the reply filed on 10/31/2007, Applicant points to paragraphs 0004 and 0099 of PGPUB 2002/0127697 for support. It is noted that the indicated passage does not provide support for such a limitation. A search of the remaining portions of the specification failed to provide literal or figurative support for LTR at either 5' or 3' end (i.e., in the alternative). The specification only provides support for a retroviral polynucleotide comprising LTRs at both 5' and 3' ends. Moreover, it is noted that a retroviral vector with only one LTR at one end could not function in the claimed invention.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or

terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Applicant points to page 64, lines 16-20, page 67, and Fig 8 as explaining that the LTR need only be present at one or both of the 5' or 3' ends and that during reverse transcription the LTR is duplicated. Accordingly, Applicant argues, delivery of a vector comprising a single LTR would be sufficiently duplicated during the RCR life cycle. Furthermore, Applicant argues, pages 18 and 19 explain the viral life cycle including that upon transcription the provirus "now" has two identical repeats at either end. Accordingly, Applicant submits that the disclosure includes support (including figurative support) for the recited phrase.

Applicant's arguments are acknowledged however, the rejection is maintained because the specification does not provide support for a retroviral vector comprising a 5' or a 3' LTR; the specification only provides support for a retroviral vector comprising both 5' and 3' LTRs. On p. 64 (lines 16-20) the specification teaches that the MoMLV proviral LTR consists of three regions, designated U3, R, and U4 and that the promoter elements controlling replication reside in the U3 region. For replication, the U3 region of

the 5' LTR initiate transcription and it is not included in the transcript (however, R and U5 regions are maintained); the transcript reads through the U3 region of the 3' LTR, which 3'LTR U3 region is re-duplicated at the 5' during reverse transcription. Therefore, it is not the claimed MLV vector, but its transcript within the transduced cells which has only 3' LTR U3 region; the claimed MLV, which is the DNA vector used to transduce the cells, has both LTRs. Fig. 8 and p. 67 of the specification teach that the probasin promoter was engineered into the U3 region of the 3' LTR, which probasin promoter will be re-duplicated in the U3 region of the 5' LTR after one round of replication; therefore, albeit the U3 region of the 3' LTR could be replaced with the probasin promoter, the 5' LTR and the R and U5 regions of the 3' LTR are present. Therefore, the teachings on p. 67 and Fig. 8 do not provide support for the complete absence of any LTR. The specification clearly contemplates the use of a vector comprising both the 5' and the 3' LTRs or at least the complete 5' LTR and the R and the U5 regions of the 3' LTR when the use of a tissue-specific promoter is envisioned. Moreover, as noted above, an MLV DNA vector could not function without both LTRs , which are necessary for integration into the host cell genome and transgene expression (see Coffin et al., first page; see also attached Fig. 1 from Coffin et al.). For these reasons, Applicant's arguments are not found persuasive, and the rejection is maintained.

Conclusion

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Coffin et al. (Retroviruses, Principle of Retroviral Vector Design,

Cold Spring Harbor Laboratory Press, 1997) and Stull et al. (U.S. Patent No. 6,322,969) were cited in response to Applicant's argument that one of skill in the art would not have extrapolated the teachings of Murakami et al. to an MLV vector. Specifically, the references teach that transgenes and IRES-comprising cassettes could be successfully inserted into retroviral vectors without affecting their replication cycle; wherein insertion could be 3' to the ENV.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Examiner, Art Unit 1633